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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,803	05/25/2001	Stephen B. Liggett	MWH-0029US	3706

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GENAISSANCE PHARMACEUTICALS
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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,803	LIGGETT, STEPHEN B.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23 and 26-29* is/are pending in the application.

4a) Of the above claim(s) *9,10,12,16-21,23 and 26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of group I in Paper No. 12 is acknowledged. Applicants comments regarding the rejoinder of groups I and III are convincing. Accordingly, claims 1-8, 11 and 13-15 have been examined herein. Applicants traverse the restriction requirement by stating that the claims of groups I, V and IX should be rejoined because the claims share a common technical feature. Applicants assert that the Edmorine reference, cited in the Office action of Paper No. 11, does not anticipate the invention of group I because the reference does not teach sequencing both copies of an individual's 5' LC and thereby cannot be used to show that the groups lack a special technical feature. Applicants further assert that there is no requirement that the claims have the same objective in order to be considered to have unity of invention. Applicants arguments have been fully considered but are not convincing. It is noted that evidence establishing that the claimed methods lack a special technical feature need not be in the form of a reference which anticipates the claimed invention. While the claims of groups I, V and IX involve a step of determining the identity of a nucleotide at position 1541 of the 5' LC, the prior art teaches sequencing the 5' LC and thereby teaches determining the identify of the nucleotide at position 1541 of the 5' LC. Accordingly, determining the identity of nucleotide 1541 of the 5' LC does not provide a contribution over the art. It is further noted that the claims of group V do not require analyzing both alleles of an individual for a polymorphism at position 1541 and that analyzing the sequence for both copies of the 5'LC would have been obvious to one of ordinary skill in the art at the time the invention was made. Lastly, it is pointed out that Applicants are entitled to the first product, method of using that product and method of making

that product. Accordingly, claims 1-8, 11 and 13-15 have been examined together, whereas the claims of groups II and IV-IX constitute additional, distinct methods.

The requirement is still deemed proper and is therefore made FINAL.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Timmermann (Kidney International. June 1998.. 53: 1455-1460).

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene (see page 1456 and Table 1). In particular, Timmermann teaches detecting either a T or a C at the -47 position. The -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -20, +46, and +79 of the β2-AR gene (see Table 1 and page 1457).

3. Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Timmermann (Journal of Molecular Medicine (May 1998) 76: B30, Abstract P109).

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles.

4. Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Timmermann (Human Mutation (March 1998) 11(4): 343-344).

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. polymorphisms at positions -1343, -1023, -654 and -20.

5. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Lenzen (WO 97/35973).

Lenzen teaches an oligonucleotide designated therein as SEQ ID NO: 27 which comprises present SEQ ID NO: 5.

SEQ ID NO:27 of Lenzen: 5'- CCGAGGTCCG CCCGCTGAGG-3'

Present SEQ ID NO: 5: 5'- GTCCG CCCGCTGAGG-3'.

It is a property of the oligonucleotide of Lenzen that it is an allele-specific oligonucleotide that specifically hybridizes to a β2-AR polynucleotide region containing the 5' LC polymorphic site.

6. Claims 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Schofield (GenBank Accession No. Y00106).

Schofield teaches an oligonucleotide comprising each of the sequences of SEQ ID NO: 6 and 8. In particular, nucleotides 740-754 of the oligonucleotide of Schofield comprise present SEQ ID NO: 6 and nucleotides 729-748 of the oligonucleotide of Schofield comprise present SEQ ID NO: 8. The oligonucleotide of Schofield is considered to be an allele specific oligonucleotide because it is fully complementary to and will hybridize specifically to the 5' LC polymorphic site.

7. Claims 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Emorine (cited in the office action of Paper No. 11).

Emorine teaches an oligonucleotide comprising each of the sequences of SEQ ID NO: 6 and 8. In particular, nucleotides 1210-1224 of the oligonucleotide of Emorine comprise present SEQ ID NO: 6 and nucleotides 1198-1217 of the oligonucleotide of Emorine comprise present SEQ ID NO: 8. The oligonucleotide of Emorine is considered to be an allele specific oligonucleotide because it is fully complementary to and will hybridize specifically to the 5' LC polymorphic site.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6-8, 11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Kidney International) in view of Green (reference "BA") and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene (see page 1456 and Table 1). In particular, Timmermann teaches detecting either a T or a C at the -47 position. The -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -20, +46, and +79 of the β2-AR gene (see Table 1 and page 1457). Timmermann does not teach amplifying the target nucleic acids using allele specific primers.

However, Green teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the method comprises using allele specific primers to amplify the β2-AR (see for example, page 26). Green teaches that the allele specific primers are designed so that the 3' end nucleotide of the primer is modified so that it is complementary to the polymorphic site (see exemplified primers of Table 1). Green teaches that this is an effective means for genotyping the

β2-AR gene and determining whether an individual is homozygous or heterozygous for the polymorphic sequence.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific primers as taught by Green in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 7 and 8 since the prior art teaches methods for designing primers that are allele specific and it was well known in the art at the time the invention was made that the sequence at the 3' end of the primer influences its ability to specifically hybridize to a target sequence and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific primers and methods of using said primers for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

9. Claims 1, 2, 6-8, 11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Journal of Molecular Medicine) in view of Green (reference "BA") and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles. Timmermann does not teach amplifying the target nucleic acids using allele specific primers.

However, Green teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the method comprises using allele specific primers to amplify the β2-AR (see for example, page 26). Green teaches that the allele specific primers are designed so that the 3' end nucleotide of the primer is modified so that it is complementary to the polymorphic site (see exemplified primers of Table 1). Green teaches that this is an effective means for genotyping the β2-AR gene and determining whether an individual is homozygous or heterozygous for the polymorphic sequence.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific primers as taught by Green in order to have

provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 7 and 8 since the prior art teaches methods for designing primers that are allele specific and it was well known in the art at the time the invention was made that the sequence at the 3' end of the primer influences its ability to specifically hybridize to a target sequence and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific primers and methods of using said primers for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

10. Claims 1, 2, 6-8, 11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation (March 1998) 11(4): 343-344) in view of Green (reference "BA") and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention.

Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach amplifying the target nucleic acids using allele specific primers.

However, Green teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the method comprises using allele specific primers to amplify the β2-AR (see for example, page 26). Green teaches that the allele specific primers are designed so that the 3' end nucleotide of the primer is modified so that it is complementary to the polymorphic site (see exemplified primers of Table 1). Green teaches that this is an effective means for genotyping the β2-AR gene and determining whether an individual is homozygous or heterozygous for the polymorphic sequence.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific primers as taught by Green in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 7 and 8 since the prior art teaches methods for designing primers that are allele specific and it was well known in the art at the time the

invention was made that the sequence at the 3' end of the primer influences its ability to specifically hybridize to a target sequence and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific primers and methods of using said primers for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 1, 2, 4-6, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Kidney International) in view of Soppet (U.S. Patent No. 5,817,477) and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene (see page 1456 and Table 1). In particular, Timmermann teaches detecting either a T or a C at the -47 position. The -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -20, +46, and +79 of the β2-AR gene (see Table 1 and page 1457). Timmermann does not teach detecting the -47 mutation using allele specific probes.

However, Soppet teaches methods for detecting polymorphisms in adrenergic receptor genes. Soppet (column 15) teaches that polymorphisms may be detected by sequencing or by first amplifying the DNA and detecting the polymorphism using allele specific probes.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific probes as taught by Soppet in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 5 and 6 since the prior art teaches methods for designing probes that are allele specific and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific probes and methods of using said probes for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

12.Claims 1, 2, 4-6, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Journal of Molecular Medicine) in view of Soppet (U.S. Patent No. 5,817,477) and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene. In

particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles. Timmermann does not teach detecting the -47 mutation using allele specific probes.

However, Soppet teaches methods for detecting polymorphisms in adrenergic receptor genes. Soppet (column 15) teaches that polymorphisms may be detected by sequencing or by first amplifying the DNA and detecting the polymorphism using allele specific probes.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using allele specific probes as taught by Soppet in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 5 and 6 since the prior art teaches methods for designing probes that are allele specific and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific probes and

methods of using said probes for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

13. Claims 1, 2, 4-6, 11, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation) in view of Soppet (U.S. Patent No. 5,817,477) and Emorine.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach amplifying the target nucleic acids using allele specific primers. Timmermann does not teach detecting the -47 mutation using allele specific probes.

However, Soppet teaches methods for detecting polymorphisms in adrenergic receptor genes. Soppet (column 15) teaches that polymorphisms may be detected by sequencing or by first amplifying the DNA and detecting the polymorphism using allele specific probes.

Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47

5' LC polymorphism by using allele specific probes as taught by Soppet in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have designed allele specific primers identical and functionally equivalent to the primers of SEQ ID NO: 5 and 6 since the prior art teaches methods for designing probes that are allele specific and because Emorine teaches the complete sequence surrounding the 5'LC polymorphic site. Accordingly, the claimed allele specific probes and methods of using said probes for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

14.Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation) in view of Large (Journal of Clinical Investigation (1997) 100: 3005-3013) and Emorine and further in view of the New England Biolabs Catalog.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach detecting the polymorphism by restriction enzyme analysis.

However, Large teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the methods comprise amplifying the β2-AR gene and detecting a polymorphism in the gene by RFLP analysis. As taught by Large, the presence of a polymorphism in a gene may introduce or remove a restriction enzyme site. The loss or gain of a restriction enzyme site may be detected by digesting the DNA with the restriction enzyme and separating the DNA by gel electrophoresis to detect a change in the length of a restriction enzyme fragment, relative to a control sample (see, for example, Figure 1). Large teaches that this methodology can be used to distinguish between individuals homozygous and heterozygous for the polymorphic sequence. Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al. Furthermore, the New England Biolabs teaches the MspA1 I enzyme and the site at which this enzyme cleaves double-stranded DNA.

In view of the teachings of Large, Emorine and the New England Biolabs catalog, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using RFLP analysis in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have selected the MspA1I enzyme as the restriction enzyme for RFLP analysis since the sequence surrounding the -47

polymorphism was taught by Emorine and computer programs were well known in the art for analyzing DNA and identifying restriction enzyme sites present in the DNA. Accordingly, the claimed methods of using the MspA1 I restriction enzyme for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

15. Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Journal of Molecular Medicine) in view of Large (Journal of Clinical Investigation (1997) 100: 3005-3013) and Emorine and further in view of the New England Biolabs Catalog.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises isolating genomic DNA from an individual, amplifying the DNA by PCR and determining the identity of the nucleotide pair at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex sequence analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at the Arg16 and Glu27 alleles. Timmermann does not teach detecting the polymorphism by restriction enzyme analysis.

However, Large teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the methods comprise amplifying the β2-AR gene and detecting a polymorphism in the gene by RFLP analysis. As taught by Large, the presence of a polymorphism in a gene may introduce or remove a restriction enzyme site. The loss or gain of a

restriction enzyme site may be detected by digesting the DNA with the restriction enzyme and separating the DNA by gel electrophoresis to detect a change in the length of a restriction enzyme fragment, relative to a control sample (see, for example, Figure 1). Large teaches that this methodology can be used to distinguish between individuals homozygous and heterozygous for the polymorphic sequence. Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al. Furthermore, the New England Biolabs teaches the MspA1 I enzyme and the site at which this enzyme cleaves double-stranded DNA.

In view of the teachings of Large, Emorine and the New England Biolabs catalog, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using RFLP analysis in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have selected the MspA1I enzyme as the restriction enzyme for RFLP analsysis since the sequence surrounding the -47 polymorphism was taught by Emorine and computer programs were well known in the art for analyzing DNA and identifying restriction enzyme sites present in the DNA. Accordingly, the claimed methods of using the MspA1 I restriction enzyme for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

16. Claims 1-3, 6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Timmermann (Human Mutation) in view of Large (Journal of Clinical Investigation (1997) 100: 3005-3013) and Emorine and further in view of the New England Biolabs Catalog.

Timmermann teaches a method for genotyping the β2-AR gene wherein the method comprises determining the identity of the nucleotide at position -47 of the 5' LC of the β2-AR gene. In particular, Timmermann teaches using multiplex cycle sequencing analysis to analyze both copies of an individual's 5' LC for the -47 mutation. It is noted that the -47 position disclosed by Timmermann is identical to the 5' LC polymorphic site of the present invention. Timmermann also teaches detecting polymorphisms at positions -1343, -1023, -654 and -20. Timmermann does not teach detecting the polymorphism by restriction enzyme analysis.

However, Large teaches methods for detecting the presence of a polymorphism in the β2-AR gene wherein the methods comprise amplifying the β2-AR gene and detecting a polymorphism in the gene by RFLP analysis. As taught by Large, the presence of a polymorphism in a gene may introduce or remove a restriction enzyme site. The loss or gain of a restriction enzyme site may be detected by digesting the DNA with the restriction enzyme and separating the DNA by gel electrophoresis to detect a change in the length of a restriction enzyme fragment, relative to a control sample (see, for example, Figure 1). Large teaches that this methodology can be used to distinguish between individuals homozygous and heterozygous for the polymorphic sequence. Additionally, at the time the invention was made the sequence of the β2-AR gene was well known in the art and is specifically taught by Emorine et al.

Furthermore, the New England Biolabs teaches the MspA1 I enzyme and the site at which this enzyme cleaves double-stranded DNA.

In view of the teachings of Large, Emorine and the New England Biolabs catalog, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Timmermann so as to have detected the -47 5' LC polymorphism by using RFLP analysis in order to have provided an equally rapid and effective means for genotyping the β2-AR gene and for determining whether an individual was heterozygous or homozygous for the 5' LC polymorphism. Additionally, it would have been obvious to one of ordinary skill in the art and well within the skill of the art to have selected the MspA1I enzyme as the restriction enzyme for RFLP analsysis since the sequence surrounding the -47 polymorphism was taught by Emorine and computer programs were well known in the art for analyzing DNA and identifying restriction enzyme sites present in the DNA. Accordingly, the claimed methods of using the MspA1 I restriction enzyme for genotyping the β2-AR gene would have been obvious to one of ordinary skill in the art at the time the invention was made.

17. Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emorine in view of Soppet and Brooks-Wilson.

The claims are drawn broadly to methods for genotyping the β2-AR gene. As written, the claims include methods which generically determine the sequence of the β2-AR gene. Emorine teaches methods of sequencing the β2-AR gene and teachings the resulting sequence of the β2-

AR gene including the leader cistron sequences (see page 6995 and Figure 1). Emorine does not teach determining the sequence of both copies of the β2-AR gene.

However, Brooks-Wilson teaches methods for detecting sequencing genomic DNA and for determining the presence of mutations and polymorphisms in DNA. IN the method of Brooks-Wilson, genomic DNA is amplified by PCR, cycle sequencing is performed, and sequences are determined and analyzed for the presence of heterozygous positions (see column 28). The method of Brooks-Wilson results in the analysis of the sequence of both copies of a genomic DNA sequence. Furthermore, Soppet teaches the importance of determining the sequence of adrenergic receptor genes and of identifying sequence variations in the adrenergic receptor genes (see, for example, columns 15-16).

In view of the teachings of Soppet and Brooks-Wilson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the β2-AR gene using the cycle sequencing method of Brooks-Wilson in order to have provided an effective means for analyzing the β2-AR gene for the presence of genetic variation. Such a method would have analyzed all positions of the β2-AR gene including the -47 5' LC polymorphic site and would have necessarily identified the nucleotide pair present at the 5' LC polymorphic site.

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hoehe et al (WO 99/37761) discloses the -47 C>T mutation in the gene which results in a Arg to Cys mutation at position 19 of the 5' LC (see page 5 and figure 1).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

December 23, 2002

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER